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Transport Processes in Biomedical Systems: A Roadmap for Future Research Directions

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Abstract—A workshop was convened at Bethesda, Maryland on May 5 and 6, 2004 under the sponsorship of the NSF and NIH with the objectives of identifying emerging intellectual opportunities and applications in biotransport sciences and of guiding future research in the field. Approximately 50 leading researchers in the fields of fluid, heat, and mass biotransport were presented forward-looking perspectives and discussed how to synthesize broad cross-disciplinary areas: this defined guidelines for a roadmap document. Applications were presented in the context of disease analysis and diagnosis, therapy and prevention, and for physiologic and engineered living systems. The roadmap prioritizes specific research thrusts that reflect projected impacts on intellectuals, medical, and biological advances. Several overarching themes emerged. Most central is the expanded integration of fundamental transport sciences into the understanding of living systems and the great potential of patient specific modeling in designing a broad array of medical procedures.

Keywords—Biotransport, Research roadmap, Prioritized research thrusts.

BACKGROUND

Interactions involving fluid mechanics, heat transfer, and mass transport in biology and medicine are pervasive in understanding the causes of disease and in the development of new prophylactic, diagnostic, and therapeutic protocols for improving human health. Mass, fluid, and heat transport processes are fundamental to virtually all aspects of life science. At the same time the analysis of transport in living tissue has broad application in normal and pathologic processes and is a basis for developing rational approaches to medical interventions. Many challenges lie ahead, numerous opportunities exist for research in biotransport, but the field, as well as our focus and range of expertise, must adapt to a rapidly changing landscape in biology.

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While some may disagree, it seems that traditional mechanics (of which transport analysis may be considered a subset), practiced as a stand-alone discipline, is approaching intellectual maturity, and the greatest possibilities for making significant further contributions lie at the intersection of mechanics with other fields of endeavor, a trend referred to as "multi-physics" research. Rational analysis in biotransport must be based on anatomically, microstructurally, and molecularly correct models, realistic constitutive properties of cells and tissues (like blood vessels, nerves, lymphatics, interstitial and cellular matrix protein structures), accurate representations of transport kinetics, and problem solutions that serve to predict experimental outcomes at a level that has a deep impact on medicine and biology. Much state-of-the-art research in biomedical engineering is based on multi-disciplinary interactions, with many investigative teams now consisting of clinicians, engineers, life scientists, and mathematicians. Thus, in charting the course of research in biotransport, it is important to account for the fact that many of the most significant advances will require both strong analysis with insight into the fundamental engineering sciences and an effective collaboration among colleagues in complementary disciplines.

The modeling and measurement of phenomena in living tissues is a field that attracts large numbers of the most talented students and young faculty. Recent advances in cell and molecular biology have identified fundamental mechanisms that govern a broad spectrum of life processes in normal physiological and diseased states. Thus, for the first time biomedical engineers have at their disposal a fundamental understanding of how living systems function mechanistically so that their arsenal of analytical and experimental tools can be applied to the rational engineering of these systems to achieve targeted results in disease diagnosis, treatment, and prevention. The tools required to carry out this work are available, and even complex biological transport processes can be addressed with increasingly sophisticated imaging, proteomic, and computational resources. The people, tools and data are in place to make progress in short order.

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The time is right for a national initiative to advance our understanding of biotransport processes in living systems to a new level that will have a major impact on important problems in biology and medicine. An effective strategy would be for the NSF and NIH to partner in nurturing the disciplines of biofluid, bioheat, and biomass transport. The NIH has major resources and a coupling to medical applications, whereas the NSF has outstanding expertise in experimentation and modeling. For example, there is precedence for such a partnership between NASA and NIH in jointly sponsoring work at the National Cancer Institute. The long-term focus of NSF divisions related to this initiative will remain scientific. There can be numerous clinical and industrial applications that derive from such fundamental research. An enhanced linkage with clinicians is important, since at present biomechanical information is not optimally translated into the clinic.

Funding agencies, particularly the NSF and NIH, must continue to support and promote these essential interactions across disciplines at all levels of basic and applied biologically and medically oriented engineering research. There will be a profound, long-term benefit to the coordination of NSF and NIH in developing large scale integrated models of human physiology. There are many fundamental questions that can be answered only by the basic science that is generated within the traditional NSF perspective. Modeling is almost always at a fundamental level that is well within the realm of traditional NSF funding, and large scale modeling will become a necessity for NIH as more and more of the complexity of biological systems is embraced. With a partnership between the basic transport sciences at the NSF and the medical applications at the NIH, the health care will move inevitably towards a more reliable, predictive practice at reduced cost.

In this scientific and medical context the NSF and NIH jointly sponsored "A Workshop on Transport Processes in Biomedical Systems" at a site near the NIH campus on May 5 and 6, 2004. The workshop was organized and led by the authors and was attended by approximately 50 of the top researchers in the biotransport disciplines from throughout the United States. Representatives were present from engineering and science academic departments, medical schools and the biotechnology industry. The meeting began with a series of five presentation—discussion cycles organized around topical themes: therapeutic applications, diagnostic applications, disease prevention, physiologic systems and engineered tissues. There were presentations for each topic from the perspectives of fluid, heat, and mass transport. The in-depth and extended discussion at the conclusion of each cycle provided an opportunity for synergistic cross-disciplinary sharing of experiences, perspectives and ideas amongst all the participants present. The final afternoon of the workshop was devoted to three discipline-defined synthesis sessions for fluid, heat and mass transfer during which priorities were defined for the future research directions that are most likely to have substantial intellectual, health care and economic impact. Specific issues that were addressed were: what is the present cutting edge of knowledge; what are the most significant problems to address; what are the important directions to pursue in the coming 5 years in the context of scientific impact (advancing knowledge for future research), medical impact (exploiting current knowledge), and economic impact (critical to achieving practical applications). The considerable aggregate output from these foregoing activities is condensed and presented with an overall evaluation in this paper.

CHALLENGES OF BIOMEDICAL SYSTEMS

The issues that will most likely drive long-range directions in biotransport research can be summarized as follows. We are now at a juncture at which a robust understanding of biological constitutive mechanisms is emerging that will enable engineers to participate in a significant way in the analysis of organic diseases as well as to design processes and devices for specific medical applications. To take advantage of this situation, we will have to obtain requisite constitutive properties for specific organs, tissues, cells, and molecules for use in analytical models and device design. We need to consider processes across multiple length scales from molecular to macroscopic. The challenge that distinguishes biological systems is tremendous complexity with its large number of genetic and biochemical variables, inherent nonlinearities, and energy and information feedback loops that govern process outcomes. Such processes are difficult to model, often incorporating multiple disparate time constants. Many important variations are patient and disease specific; models must account for all of these individual factors in order to be effective for clinical protocol design.

THE ROADMAP

One of the primary outcomes of the workshop is a set of clear and strong research priorities that are common to all three of the biotransport disciplines. The cutting edge of intellectual discovery has been focused at the molecular scale, but major future advances will require integration of analysis and experiments across the full spectrum of length scales that lead to clinical applications. There is much to be gained by discovery and control of the molecular effects that govern the macro phenomena of biotransport.

Acquisition of patient specific data and constitutive properties will enable building analytical models for planning and delivery of treatment for many diseases. Development of the tools to facilitate these processes should be a high priority. Major challenges to implementing this capability include devising instrumentation to acquire the requisite patient specific data and to build models

capable of incorporating the detail necessary to incorporate the array of individual effects that direct the clinical outcomes.

A majority of the problems of greatest impact involving biotransport have a highly multidisciplinary theoretical foundation. Success in defining, addressing, and solving these problems will require collaboration via teams drawing from engineers representing multiple disciplines, life scientists, physicists, chemists, computer scientists, mathematicians, and medical scientists and clinicians. Research in biotransport phenomena can benefit from the expertise of other biomedical disciplines such as imaging, nanofabrication, biomaterials and bioinstrumentation. Collaborations among colleagues from these disparate fields can be highly synergistic and should be viewed favorably in funding agency priorities.

Many important biomedical problems can be addressed most effectively via a coordination of NSF and NIH in developing integrated models of human physiology across relevant scales bridging from basic understanding to clinical application. There are many fundamental questions of tremendous potential impact for health care that can be answered only by combining the strengths of basic science that derives from the traditional NSF research perspective with the NIH expertise in disease diagnosis, therapy and prevention.

The major challenge for the coming decade is to develop an integrative understanding of biotransport processes and their consequences from the molecular to cellular to organ levels, incorporating the subtleties of biological feedback and cross domain coupling, that can be applied to the design of devices and methods that can be translated to clinical applications and to the advance of bioscience.

DOMAIN-SPECIFIC ROADMAP GUIDELINES

In the context of the current perspectives and understanding of the leaders who participated in the workshop, explicit biotransport research topics were identified and prioritized based on their potential intellectual and medical impact. The individual research topics considered worthy of attention and support are presented in their order of ranking by the participating experts.

Bioheat Transfer

Proteomics discoveries will drive the understanding of heat transfer phenomena at the cellular level since the relevant molecular-scale processes are all governed by energy flows. It is important to understand how injury results from, and can influence, these cell-level processes. Thus, there is a strong need for a mechanistic biothermodynamic model to describe the bioheat processes, including blood perfusion effects, that occur within the cell and tissue environment. Recommended specific research projects include the following:

(1) Define the molecular thresholds for thermal injury to living systems, incorporating an understanding of the mechanisms of kinetic processes and the limits of reversibility (healing processes).
(2) Develop a model for perfusion blood flow response to thermal stress in both normal and pathological tissues.
(3) Devise real time thermal monitoring and feedback control methods specific to energy processes and apply to specific physiological systems to accomplish targeted results.
(4) Build devices for noninvasive and minimally invasive thermometry and heat flux measurement with clinically useful resolution of temperature, time, and 3D space.
(5) Develop living model systems for testing fundamental questions of biotransport and to address features such as: ability to incorporate special state indicators in a system lacking other biological complexity; scales from molecular to cellular to tissue to organ; benchmark of the behavior of complex biosystems.
(6) Develop instrumentation for measurement of thermophysical properties relevant to constitutive models of biological systems over a range of states (defined, for example, in terms of -200 to $+250^{\circ}$C, chemical composition, level of hydration, presence of various modes of stress) for thermal therapies, including optical, acoustical, electrical, thermal, magnetic, and mechanical over scales from molecular to macroscopic.
(7) Achieve an understanding of the molecular thermodynamics of crowded polymer systems in the context of environmental stress factors.
(8) Devise methods to control effects of thermal gradients in time and space on biological systems (heat transfer), including influences on the temperature field that can be coupled with: various cross-energy domain phenomena (such as chemistry, electricity, magnetism, optics); heterogeneity of state space in time, space, and biological structures; orders of magnitude of scale differences that occur in living system processes.
(9) Define methods for determination and planning of optimized doses for thermal therapy in specific target and/or organ systems.
(10) Translate the outcomes of bioheat transfer research into clinical practice and embed them into engineering and medical educational programs.

Biofluid Transfer

Fluid flows are encountered throughout physiological systems and are critical in healthy and diseased processes. Biofluid mechanics is undergoing recognition as an important component of many physiological and pathological processes and is therefore gaining interest and acceptance in many *biomedical and clinical* research areas. Biological flows are characterized by a large variation in the length scales encompassed (with a range of relevant Reynolds numbers) and different mechanisms at play (convection, both steady and oscillatory, and diffusion, reflecting variations in Strouhal and Schmidt numbers). In addition, the fluids themselves are characterized, in some cases, by complex and nonlinear constitutive behavior. Examples are as follows:

(1) Improve imaging modalities (e.g. ultrasound, magnetic resonance imaging, microvascular imaging) to identify time resolved velocity fields that reveal flow phenomena which could be used as diagnostic process tools.
(2) Study blood flow in the major arteries in relation to the hemodynamic stresses that play a role in the initiation of atherosclerosis, aneurysms, and the disruption of diseased plaques and identify the hemodynamic environment in susceptible versus athero-protected segments, in health and disease, with translation into clinical practice.
(3) Study flow in the microcirculation, lymphatics, cerebral spinal fluid and other specialized fluid compartments of specific organs based on realistic anatomical models and biomechanical properties.
(4) Define relationships between blood flow, fluid mechanical stresses, cellular mechanotransduction, and vascular restructuring in health and disease.
(5) Develop multi-scale models that bridge macroscopic flow phenomena with molecular and cellular responses.
(6) Integrate coupling flow and transport analysis with existing models of intracellular signaling, specifically to develop methods that interface between continuum fluid/transport analysis and molecular biophysics.
(7) Create simulation based disease treatments for planning surgical, endovascular, and pharmacologic therapies and for design and optimization of replacement of tissues and organs.
(8) Design therapeutic endovascular devices to address specific disease states.
(9) Model flow and clearance of biologically specialized systems (e.g. mucus within the respiratory system, intestinal peristalsis and absorption, renal and urether transport) in normal and diseased states.
(10) Integrate blood flow field physics in cardiovascular function and disease and noninvasive measurement thereof with realistic and organ specific anatomical features and biomechanical properties.
(11) Design *in vitro* experiments that critically test the most dominant fluid dynamics characteristics that exist *in vivo,* and test the conclusions by experiments *in vivo* or in intact tissues.

Biomass Transfer

Mass transport processes likewise occur in virtually all biological processes and across scales of identification and modeling from molecular to organ, playing critical roles in both normal healthy processes and in numerous disease and injury states. Although mass transport has been studied for many years, there remains a broad spectrum of phenomena for which significant contributions remain to be made. Specific examples are as follows:

(1) Create both patient-specific and generic mass transport models in combination with system-level plus molecular and cellular imaging methods.
(2) Develop organ specific formulations, testing, and verification of predictive tissue transport models in human disease (inflammation, tumors, cardiovascular, genetic, degenerative, metabolic diseases).
(3) Develop novel non-invasive techniques for detection of organ-specific transport during the inflammatory processes in man.
(4) Identify mechanisms and measurement tools associated with breakdown of biological barrier functions in disease and develop diagnostic and therapeutic approaches.
(5) Create mass transfer models for organ-specific drug, gene and stem cell therapy.
(6) Incorporate biomicro-electro-mechanical systems into diagnostic and therapeutic approaches for manipulation of small quantities.
(7) Describe the phenomenology of molecular motion (gas, liquid) around and inside nanoscale systems for medical applications.
(8) Characterize quantitatively molecular transport systems within cells that organize and move organelles within the cytoplasm and nucleus.
(9) Analyze mass transport at the interface with biological sensors for long-term function in living tissues.
(10) Understand and model cell and mass transport during embryonic development and growth.

General Biotransport Phenomena

Some of the research initiatives identified are broader than can be defined by one of the three transport subdomains, as given below:

(1) Devise methods to use transport-generated stress to modulate pathways for gene expression, apoptosis and cell necrosis, including reversing natural processes.
(2) Create and apply non-invasive instrumentation for detection and measurement of biotransport phenomena such as blood flow, and heat flux, and develop new types of generic instrumentation that can be used across a number of fields of biomedical applications.
(3) Develop phenomenological models with a critical contribution to understanding and explaining the biological, biochemical, physical, and mechanical factors that arise in various normal and diseased life processes and states.

DISCUSSION

Although participants in the workshop represented three different focus areas of biotransport research, it was apparent that a number of overarching themes emerged that are common to all the areas and that define global opportunities for achieving major intellectual and clinical impact within the coming decade. One of these areas is the development of coordinated, complementary patient-specific measurement and modeling over a broad range of health states and functions. For example, surgical, endovascular, and pharmacologic therapies used in the treatment of cardiovascular diseases attempt to restore blood flow and normal barrier functions to compromised organs and tissues. Ideally, these therapies result in sufficient blood flow at appropriate physiologic pressures while avoiding adverse flow conditions such as flow recirculation and stasis that may lead to procedural failure and/or poor outcomes. Unfortunately, the efficacy of alternate treatments cannot be tested in patients, and physicians do not have the tools needed to evaluate the multiple options or to design optimal corrective procedures. Rather, the current paradigms for medical planning rely on diagnostic data and biophysical measurements to define the present state of the patient, empirical data to evaluate the efficacy of prior treatments for similar patients, and the judgment and experience of the physician to decide on a preferred treatment. However, these inputs are insufficient to predict the outcome of a given treatment for an individual patient due to anatomic and physiologic variations and system complexity. An alternative approach for clinical decision making could be based on a predictive medicine paradigm in which a physician utilizes computational tools to construct and evaluate a combined anatomic/physiologic model based on diagnostic and empirical data to predict the outcome of alternate treatment plans for an individual patient. The result should be a therapeutic regimen designed explicitly to meet the individual medical needs of a particular patient's current disease state.

Another benefit of the integrated outcomes of the biotransport research roadmap should be the ability to better understand biological complexity of disease states. Commonly, an intervention treats or addresses symptoms of disease, particularly when the aim is palliation or treatment. However, a possible complication may arise. Deleterious effects of diseases may be offset, at least in part, by side-effects of some of the very same disabling characteristics of the disease, or by other changes associated with the disease. Selected diseases can be investigated to determine the means the body uses to compensate for malfunctioning or dysfunctional elements or processes in an attempt to maintain homeostasis. This would help to discern the parameters which govern the course of the disease and how the severity of the disease is related to the quantitative values of such parameters. This would also allow one to evaluate the efficacy of different approaches to diagnosis and treatment.

A further area of probable broad impact of the biotransport research roadmap is in simulation-based medicine. For a range of human diseases and afflictions, there is a significant opportunity to develop problem solving environments for predicting outcomes of possible interventions based on patient-specific anatomic and physiologic data and simulation-based methods. This could revolutionize medical practice by infusing an engineering approach into therapeutic decision-making. In addition to enabling physicians to devise better treatments, simulation methods could enable medical device manufacturers to predict the performance in virtual patients prior to deployment in animal studies and human trials. The most important research needs in predictive medicine include the following:

(1) Multiscale/multiphysics/multisystem algorithms and data structures: Arguably the most critical need for the development of simulation-based medicine is in formulating biophysical and biochemical realistic simlation algorithms and data structures that span the physical and temporal scales, relevant physics and organ-systems.
(2) Imaging-to-models process: A fundamental technology in predictive medicine is the creation of patient-specific and generic models from system-level and molecular and cellular imaging methods.
(3) Simulation-based design of medical devices: At all spatial scales and across these scales, the development of simulation-based design "problem-solving environments" for specific technologies could have an immediate and significant impact in the medical device industry.
(4) Simulation-based design of replacement tissues and organs: For many tissues, including blood vessels,

bones and muscles, structural-integrity, mass-transport and biological-viability design criteria must be addressed. For other organ systems, e.g. replacement kidneys, livers and lungs, the nutrition and transport functions of these replacement organs represent daunting design challenges. It is clear that simulation methods applied to the biotransport sciences will be necessary for the design and optimization of replacement tissues and organs.

Realization of these integrated applications will depend on success in numerous of the specific biotransport research initiatives listed in the roadmap. Key requirements for long-term successful implementation of strategic planning for research directed to these new pathways of discovery is to entice established faculty in different disciplines to collaborate by incentives (funding) and to introduce and sustain interdisciplinary training early in the careers of students without compromising depth and rigor in a primary discipline. The NIH Roadmap proposes both approaches and in addition redefines the role of universities by encouraging centers of technical biomedical excellence.

SYNOPSIS

The basis of biological and medical processes in their enormous richness is coming to light with establishment of the molecular-genetic basis of life processes. Biology has become the new basic science. The challenge and opportunity for heat, fluid and mass transfer processes to be understood at this level are large. Each biological problem, as small as it may be, is a city of events to be analyzed. Nature utilizes stereotypic processes well tested over time; the challenge is to recognize and formulate these underlying principles. Transport processes are at the heart of biology and medicine at every stage of life. We need to integrate biological processes of gene expression and protein synthesis into modern transport theory. The failure of transport processes in human disease need to be identified. In turn, transport analysis of living tissues will serve to innovate and optimize diagnostic and therapeutic interventions.

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